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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,761	01/14/2004	Laurence S. Harbige	604-706	1504

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
10/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,761	HARBIGE ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-11 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1-3,6-11,14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/19/2010 has been entered.

Claims 1-3, 6-11, and 14-16 are examined herein, insofar as they read on the elected invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 11, 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bountra et al. (WO 00/61231, PTO-1449).

Bountra et al. discloses a method of treating multiple sclerosis comprising administering sodium channel antagonists such as 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine called lamotrigine, 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine, and compounds of formula (II) with C1-4 alkyl substituents or CF3 groups. See page 7, lines

20-24; page 8, lines 5-10; page 14, claim 7; page 1, lines 15-19; page 3, lines 9-12. Bountra et al. teach that the suitable dose range is for example 0.1 mg/kg to 30 mg/kg bodyweight per day. A dose range of sodium channel antagonist is 200 mg/day to 900 mg/day for an adult human. See page 10, lines 1-8. Bountra et al. also teaches that it may be necessary to make routine variation to the dosage, depending on the age and condition of the patient. See page 10, lines 1-8.

Bountra et al. does not explicitly teach administration of lamotrigine in the method of treating multiple sclerosis i.e does not provide an example.

Bountra et al. does not teach 1, 2, 4-triazine compounds with alkyl substituents such as methyl, ethyl as in claim 16.

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer lamotrigine to treat multiple sclerosis because Bountra et al. teach that sodium channel antagonist such as lamotrigine are useful in treating multiple sclerosis. Accordingly, one of ordinary skill in the art would have been motivated to administer lamotrigine with reasonable expectation of success of treating multiple sclerosis.

Further, regarding the recitations, “wherein the therapy results in reduction of one or more of incidence of relapse, spasticity and fatigue”, “wherein the therapy stabilizes the patients Expanded Disability Status Score, thus halting progress of the disease”, in claims 8-9, since Bountra et al. render the claimed method of administration of effective amounts of lamotrigine for treating multiple sclerosis obvious, administration of lamotrigine necessarily results in reduction of one or more of incidence of relapse, spasticity and fatigue”, halts progress of the disease, as claimed herein.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ triazine compounds containing alkyl substituents in the method of treating multiple sclerosis because Bountra et al. teach structurally similar diazine compounds containing C1-4 alkyl substituents, and trifluoromethyl groups as sodium channel blocker, useful in the methods of treating multiple sclerosis. Accordingly, one of ordinary skill in the art at the time of invention would have been motivated to the instant particular triazine compounds containing C1-4 alkyl substituents or trifluoromethyl groups with reasonable expectation of employing them in the method of treating multiple sclerosis.

Claims 10, 14-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bountra et al. (WO 00/61231, PTO-1449) as applied to claims 1-3, 6-9, 11, 16.

Bountra et al. is applied as discussed above.

Bountra et al. discloses a method of treating multiple sclerosis comprising administering sodium channel antagonists such as 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine called lamotrigine, 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine. See page 7, lines 20-24; page 8, lines 5-10. A dose range of 200 mg/day to 900 mg/day for an adult human is disclosed. Bountra et al. also teaches that it may be necessary to make routine variation to the dosage, depending on the age and condition of the patient. See page 10, lines 1-8.

Bountra et al. does not specifically teach the amount of lamotrigine as 600 mg/day as in claim 14, and the dosing regimen as in claim 15.

It would have been obvious to a person of ordinary skill in the art at the time of invention to determine or optimize parameters such as effective amounts of lamotrigine to be administered in the method of treating multiple sclerosis.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 11, and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lunardi et al. (Neurology, volume 48(6), 1997, pages 1714-1717, PTO-892).

Lunardi et al. discloses administration of lamotrigine to patients suffering from multiple sclerosis in which trigeminal neuralgia was also present. See abstract; page 1715. Lamotrigine was administered at an initial dosage of 25 mg/day, increasing in increments of 25 mg every third day up to a dosage of 400 mg/day. See page 1716, left hand column. Administration of lamotrigine to patients suffering from multiple sclerosis concomitant with trigeminal neuralgia resulted in complete pain relief.

Lunardi et al. does not specifically teach the specific amount of lamotrigine as between 500 mg/day and 700 mg/day.

It would have been obvious to a person of ordinary skill in the art at the time of invention to determine or optimize parameters such as effective amounts of lamotrigine to be administered in the method of treating multiple sclerosis.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Further, regarding the recitations, "wherein the therapy results in reduction of one or more of incidence of relapse, spasticity and fatigue", "wherein the therapy stabilizes the patients Expanded Disability Status Score, thus halting progress of the disease", in claims 8-9, since Lunardi et al. render the claimed method of administration of effective amounts of lamotrigine for treating multiple sclerosis obvious, administration of lamotrigine necessarily results in reduction of one or more of incidence of relapse, spasticity and fatigue", halts progress of the disease, as claimed herein.

Response to Arguments

Applicant's arguments, and the Declaration of Dr. Jacqueline Palace filed on 04/19/2010 have been considered, but not found persuasive.

The Declaration of Jacqueline Palace states that "As a physician having extensive knowledge and experience of MS, I do not agree that patients should be prescribed lamotrigine at doses as high as 900 mg. I base this statement on my review of the doses tolerated in Dr Kapoor's recent lamotrigine trial in secondary progressive MS, where the highest tolerated dose was 300 mg (average only 78 mg) in this

population. Indeed, the protocol stated a maximum dose of 400 mg, and I note that this was the maximum dose in the Lunardi study". These remarks have been considered, but not found persuasive. The declaration under 37 CFR 1.132 has been fully considered but is ineffective to overcome the 103(a) rejection herein as to nonobviousness over the prior art, since the declaration merely presents statements, conclusion or speculations or opinions regarding the claimed invention, i.e., the doses tolerated in Dr Kapoor's recent lamotrigine trial in secondary progressive MS, where the highest tolerated dose was 300 mg lysergol, but fails to set forth any factual evidences. Therefore, the declaration is insufficient to rebut the prima facie case herein. It is pointed out that applicant did not provide the cited Dr. Kapoor's reference.

Applicant's arguments with respect to side effects have been considered. It pointed out that Guberman et al. teaches that the prescription of lamotrigine, as with all other drugs should be undertaken with appropriate consideration of the potential risks to the patient in relation to potential benefits i.e one needs to exercise caution in using lamotrigine as with any other drug. See page 989 of Guberman et al.

Applicant's remarks regarding papers such as Leandri et al., Solaro et al., Silver et al., Titlie et al. etc., it is pointed out that the papers cited do not state that the maximum dose one can employ in the treatment of multiple sclerosis is 400 mg/day of lamotrigine. For example, it is pointed out that Solaro et al. reference (Neurol Sci 2005), provides data for administration of lamotrigine at 150 mg.day, and 170 mg/day only. From, the data provided by Solaro one cannot conclude that the maximum tolerated dosage is 400 mg/day, since no where does Solaro et al. teach that. The same is true for the papers such as Leandri et al., Silver et al., Titlie et al. etc.

Bountra et al. clearly discloses that sodium channel antagonists which includes lamotrigine are used for treating multiple sclerosis. Bountra broadly teaches a dose range of sodium channel antagonists therein which include lamotrigine as 200 mg/day to 900 mg/day for an adult human. It would have been obvious to a person of ordinary skill in the art at the time the invention to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art, and further Bountra teaches that it may necessary to make routine variations to the dosage. One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Applicant's arguments, and the Declaration of Professor Giovannoni filed on 05/25/2010 have been considered, but not found persuasive as discussed below.

Applicant's remarks that "Professor Giovannoni declares that in his opinion, at the time of the present invention, an experienced neurologist in this art such as himself would not have contemplated administering LTG to a patient suffering from MS in dosage levels higher than the recommended maximum of 400mg daily. Professor Giovannoni's reasoning (paragraph 8) is that LTG is neuroprotective in animal models of global and focal ischaemia *in vivo* at doses of 20mg/kg and above, i.e., greater than 4X the anticonvulsant dose in rats (although the ED50 is 2mg/kg, the rat anticonvulsant ED95 is approximately 5mg/kg." These remarks have been considered. First, it is

pointed out that the cited references do not teach that one should not use LTG at a dosage higher than 400 mg/day in treating multiple sclerosis. Second, Professor Giovannoni teaches "LTG is neuroprotective in animal models of global and focal ischaemia *in vivo* at doses of 20mg/kg and above" i.e for a 60 kg human it is 1200 mg. Thus, one can employ greater than 400 mg/day of LTG.

Applicant argues that "In paragraph 12, the Giovannoni declaration states that doses of LTG lower than 400mg per day have been used to treat central pain in patients with MS, and that in the paper by Leandri and colleagues (Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis, Leandri et al., 2000. iNeurol. 247:556-558), doses of 25mg daily to a maximum of 400mg daily were used." These arguments have been considered, but not found persuasive because Leandri et al., does not teach that one should not use LTG at a dosage higher than 400 mg/day for the treatment of multiple sclerosis. Leandri teaches that complete pain relief resulted at doses between 75 and 400 mg/day, and thus suggests that a maximum dosage of 400 mg/day is sufficient for the treatment therein which is trigeminal neuralgia pain.

Applicant argues that "In paragraph 16, Professor Giovannoni concludes that, in light of the published facts prior to the present invention and the subsequent US patent filing in 2004, it would not have been obvious to him or any other neurologist with skill in the art of administering LTG that doses higher than the recommended maximum of 400mg daily could be effective to modify the course of the progressive pathology of MS to the extent exhibited in the patent application." These arguments have been considered, but not found persuasive because the published facts cited by applicant do not teach that one should not use LTG at a dosage higher than 400 mg/day in treating

multiple sclerosis. Bountra et al. clearly discloses that sodium channel antagonists which includes lamotrigine are used for treating multiple sclerosis. Bountra broadly teaches a dose range of sodium channel antagonists therein which include lamotrigine as 200 mg/day to 900 mg/day for an adult human. It would have been obvious to a person of ordinary skill in the art at the time the invention to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art, and further Bountra teaches that it may necessary to make routine variations to the dosage. One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Further, Applicant's declarations under 37 CFR 1.132, are insufficient to overcome the rejection under 35 U.S.C. 103(a) for the following reasons. It has been held that any unexpected/surprising results submitted to rebut the prima facie case, the scope of the showing must be commensurate with the scope of the claims. *In re Coleman*, 205 USPQ 1172; *In re Greenfield*, 197 USPQ 227; *In re Lindener*, 173 USPQ

356; *In re Payne*, 203 USPQ 245. Note that the claims include several compounds of formula I, and not just lamotrigine.

Applicant argues that "Lunardi likewise does not suggest treatment of multiple sclerosis using the claimed dosage level. Thus, taking Bountra alone, or in combination with Lunardi, the physician would not have been motivated to arrive at the presently claimed dosage of between 500mg/day and 700mg/day and, in fact, would have acted to reduce the dosage in the case of multiple sclerosis patients based on the state of the art." These arguments have been considered, but not found persuasive as discussed above. One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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